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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,210	03/27/2001	Shlomo Margel	LUZZ-051CIP	7952

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LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK
600 SOUTH AVENUE WEST
WESTFIELD, NJ 07090

EXAMINER

SHARAREH, SHAHNAM J

ART UNIT	PAPER NUMBER
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1617

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/701,210

Applicant(s)

MARGEL ET AL.

Examiner

Shahnam Sharareh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 December 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-46 is/are pending in the application.
- 4a) Of the above claim(s) 33-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 33-46 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3. 6) ☐ Other: _____

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DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in Paper No. 8 is acknowledged.

Claims 33-46 are withdrawn from further consideration pursuant to 37 CFR

1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Applicant traversals on the election of species have been fully considered, but not persuasive. However, to expedite the prosecution, Examiner withdraws said requirement. Claims 1-32 are under consideration.

2. This application contains claims 33-46 drawn to an invention nonelected with traverse in Paper No. 8. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 23-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are rejected under 35 U.S.C. 112, first paragraph, because the specifications, while being enabling for methods of preparing magnetic particles

comprising mixing an aqueous solution of polymeric metal chelating agent with sufficient amount of a metal salt wherein said metal salt is able to form an oxide with magnetic properties at its oxidation state, do not reasonably provide enablement for methods of making hollow nanoparticles by "burning off the polymeric material." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim.

Ex parte Forman (230 USPQ 546, BdPatApp & Int.) and *In re Wands* (858 F.2d 731, 8 USPQ2d 1400, 1404, Fed. Cir. 1988) provide several guidelines when determining if the specification of an application enable the skilled artisan to practice the invention without undue experimentation. Having such factors in mind, the instant specifications fails to allows the skilled artisan to practice the invention without undue experimentation.

The state of the prior art concerning methods of forming a hollow nanoparticle, a microcapsules, microparticle or microspheroids that can be magnetically responsive employs such methods as coacervation, sonication, polymerization with crosslinkers in the presence of magnetite, redox porlymeriztions, encapsulation, ferric platting, etc.. that leads to entrapment of gas inside the particles of interest and further using such particles comprising functional groups that are able to bind with metal salts (see US Patent 4,77,265 col 1-2; also EP 0180384 pages 2-5). However, the disclosure of instant application of making hollow nanoparticles comprising "burning off the polymeric material of a solid particle" does not describe the functional correlation between the

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burned off nanoparticles and the nanoparticles that do not undergo the step comprising burning the polymeric material by a device producing high temperatures.

In this case the molecular integrity and functionality of the produced hollow nanoparticles that undergo the disclosed burning step is not predictable, and further one skilled artisan will not be able to determine whether a bioactive agent such as an antibody, an enzyme or a chemical entity is able to crosslink to said nanoparticle after portion of its internals have been burned off. Moreover, biocompatible dispersing microspheres or polymeric shells or microbubbles known in the art may comprise of any chemical entity that do not appreciably alter or affect in any adverse way, the biological system into which they are introduced; the characteristics that is not well know in the art about compositions comprising burned polymers of gelatin, dextran, chitosan, polylysine or other claimed polymeric entities.

In addition, there is not prior knowledge whether such hollow nanoparticles are incapable of inducing any immune response or whether they require any specific biocompatible coating before administration. Therefore, there is no predictability in the art concerning the methods of making and using hollow nanoparticles made by burning off the polymeric portion of the claimed nanoparticles.

Further, there is no correlation between the working example describing the method of making and using the non-hollow nanoparticles and the hollow nanoparticles. Therefore, the amount of guidance presented in the specification fails to present a required amount of guidance to perform the claimed method without undue

experimentation, and without such information, one skilled in the art could not determine the utility of the claimed compositions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 19-20, 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

Claims 19-20 respectively recite limitations "portionwise mode of operation as herein before define" and "a continuous mode of operation as hereinbefore defined." First it is not clear what is meant by "portionwise or continuous mode." Second it appears that these phrases lack sufficient antecedent basis. It is not clear to which "hereinbefore" step is Applicant referring.

Claim Objections

Claim 1 and 25 are objected to because of the following informalities:

- Claim 1 is confusing because it is not clear whether the steps of the instant method is to occur sequentially or whether the order of the steps, if altered, will compromise the uniformity of the claimed particles.
- The recitation of claim 25, wherein "n is an integer between 1to 18, inclusive, and X..." is ambiguous. It is not clear what is meant to be inclusive?

Appropriate correction is required.

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-32 are rejected under 35 U.S.C. 103(a) as being unpatentable Siiman et al US Patent 5,248,772, Ugelstad et al US Patent 4,774,265, or Margel et al US Patent 4,783,336, in view of Remington: the Science and Practice of Pharmacy 1995 p.

441-443, 583, Callewaert et al, p. 302-303 (Basic Chemistry General, Organic, Biological, Worth Publishers, Inc. 1980) and Vasconelos et al European Polymer Journal 1997 33 (5): 631-639).

The instant claims are directed to methods of preparing magnetic particles comprising

- mixing an aqueous solution of polymeric metal chelating agent with sufficient amount of a metal salt wherein said metal salt is able to form an oxide with magnetic properties at its oxidation state,
- keeping metal ions in the oxidation state,
- maintaining the pH above 7 during the process,
- keep adding metal salts to the solution to obtain monodispersed nanoparticles coated with magnetic metal oxides.

Examiner views the final step of the instant claim 1 to encompass conventional titration assay employed in the art of analytical chemistry, wherein an acid or base is added to a base or acid in incremental or dropwise fashion.

Ugelstad et al disclose a method of preparing porous magnetic particles comprising mixing an aqueous solution of polymeric metal chelating agent (e.g. methacrylic amide which can bind to the iron salts, and other copolymer set forth in col 22, lines 3-25) with sufficient amount of a metal salt ($\text{FeCl}_2/\text{FeCl}_3$) solution while maintaining the metal in its oxidation state at the presence of an oxidizing agent, and further maintaining the pH above 7 during the process (see col 2 lines 6-68, col 3-4, col 6 lines 9-68, col 9 example 1,2 & 3, col 14-15 & 17 examples 12, 13, 17-18, and col 21-

22). Accordingly, Ugelstad essentially teaches all method steps of instant claim 1-32, except that it does not explicitly teach successively repeating the instant steps d to f of the claim 1.

Siiman et al disclose a method of preparing uniform colloidal magnetic particles comprising mixing an aqueous solution of polymeric metal chelating agent (e.g. dextran, gelatin type A and B, etc.) with sufficient amount of a metal salt (FeSO_4) while maintaining the metal in its oxidation state at presence of KNO_3 , and further maintaining the pH above 7 during the process (see col 5 lines 1-43, col 6 lines 4-59, col 7-8.)

Siiman et al also disclosed colloidal particles comprising a polymer containing a metal chelating agent coated with polymers such as gelatin, and dextran coupled to a bioactive agent such as an enzyme, a protein or an antibody (see col 3 lines 45-68, col 4 lines 1-8.) Accordingly, Simmon teaches all method steps of instant claim 1-32, except that it does not explicitly teach successively repeating the instant steps d to f of the claim 1.

Margel's teaching is essentially similar to Ugelstad's except that it uses a different type of polymeric unit. Accordingly, Margel discloses methods of preparing an acrolein type particle comprising mixing an aqueous solution of acrolein with an aqueous dispersion of Fe_3O_4 in presence of an oxidizing agent at pH values above 7 to form magnetic particles of uniform size, wherein said microparticles are cross linked to various bioactive agents such as immunoglobulin or fluorescent dyes for various utilities such as cell labeling, cell separation, diagnostic purposes, etc.. (see col 1, lines 10-62, examples 1-8, and claims 1, 4-13). Margels also teaches all method steps of instant

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claim 1-32, except that it does not explicitly teach successively repeating the instant steps d to f of the claim 1.

Remington's, Callewaert and Vasconcelos are collectively used to show titration methodologies known in the art to maximize complexation and safety properties of a polymeric moiety. For example, Calleawert sets forth the general process of titration to determine appropriate concentrations of acid or base that would provide a desirable end results (see Calleawert pages 302-303, figure 11-6). This method employs small increments or dropwise addition of a base to an acid solution.

Remington further discusses "potentiometric titration" which is a known method to used in the art in assessing degree of precipitation or complexation in solutions employing insoluble or undissociated metal salts. This method is frequently used in determining the binding capacity of chelating agents comprising monitoring the pH of the solution during the mixing process. (see Remington at pages 441-442, 444, 583).

Vasconcelos is used to specify that potentiometric titration is conventionally employed in polymer industry to demonstrate the affinity of various metals such as copper to natural to synthetic polymers for biological use (se Vasconcelos at abstract, page. 632 entire 1st col, 633 1st-2nd col, 637-638).

Siiman, Ugelstad, Margel, Vasconcelos, Remington and Calleawert teach methods of preparing magnetic particles and basic laboratory methodologies; therefore, they are viewed as being in the same field of endeavor.

Again, Examiner takes the position that instantly claimed step (g) essentially reads on "potentiometric titration." Accordingly, eventhough Siiman, Ugelstad or Margel

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fail to teach the instant repeating steps (g), it would have been obvious to one ordinary skilled in the art at the time of invention to employ such titration method and add the metallic solutions of Siiman, Ugelstad or Margelof in dropwise fashion into their polymeric, because as shown by Remington and Vasconcelos and Callewaert, such method is conventionally used in the art to assess maximize complexation between a polymeric moiety and a metallic ion. Furthermore, as shown by Vasconcelos, the ordinary skill in the art would have had a reasonable expectation of success in accessing the specificity and toxicity properties of natural and synthetic polymers for biological or medical applications. m

Finally, potentiometric titration is a known method that is frequently used for determining the binding capacity of chelating agents, therefore, it would have been obvious to one ordinary skilled in the art at the time of invention to monitor the binding capacity of the polymeric metal chelating agents of Ugelstad et al or Margel et al or Siiman et al and further in view of the teachings of Remington: the Science and Practice of Pharmacy, and Vasconcelos et al to improve the methods of making nanoparticles by creating less toxic and more uniform nanoparticles.

Conclusion

No claims were allowed. Examiner points out that polymeric iron coated nanoparticles thought by Siiman, Ugelstad, Margel, Vasconcelos, Remington and Calleawert would provide similar activity as those disclosed in the specifications of the instant application, and accordingly, one skilled in the art would have known how to make and use the therapeutic composition. However, when the intended nanoparticles

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is not as described Siiman, Ugelstad, Margel, Vasconcelos, Remington and Calleawert, and further employs a "burning off" step, the final therapeutic product would not be expected to be a nanoparticle as disclosed, and furthermore, the applicant has provided no guidance or working examples teaching one skilled in the art how to make and use which type of nanoparticles would yield from the claimed invention. Therefore, based on the state of the prior art, lack of guidance and working examples, and the wide breadth of the claims 19-20; one skilled in the art could not use the entire scope of the claimed invention without undue experimentation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 703-308-1877. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.


RUSSELL TRAVERS
PRIMARY EXAMINER
GROUP 1200